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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/024,648	12/19/2001	Heather J. Belmont	49663 (71758)	2636

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 06/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

S/A

Office Action Summary	Application No.	Applicant(s)	
	10/024,648	BELMONT ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-113* is/are pending in the application.

4a) Of the above claim(s) *9-29,32-37 and 48-111* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,30,31,38-47,112 and 113* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 May 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response to the restriction requirement received on 3/29/04 has been entered. Claims 1-113 are pending in the instant application. Applicant's election without traverse of the subject matter of Group I, and further the species of "transgenic mouse" is acknowledged. As a result of applicant's election, claims 9-29, 32-37, and 48-111 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3/29/04. Claims 1-8, 30-31, 38-47, and 112-113 are currently under examination. An action on the merits follows.

Please note that claims 1-8, 30-31, 38-47, and 112-11 have only been examined to the extent that they read on the elected subject matter.

Claim Objections

Claims 4-8, 30-31, and 42-47 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependant claim. See MPEP § 608.01(n). Accordingly, the claims 4-8, 30-31, and 42-47 have not been further treated on the merits.

Please note, however, that in the interests of compact prosecution, the subject matter of the objected claims, claims 4-8, 30-31, and 42-47, have been considered for the purposes of prior

art and enablement based on the claim limitations as best as they can be interpreted in view of the improper multiple dependency of these claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7, 30-31, 38-39, 42-47, and 112 are rejected under 35 U.S.C. 103(a) as being unpatentable over 5,859,312 (1/12/99), hereafter referred to as Littman et al. in view of Mombaerts et al. (1993) Cell, Vol. 75, 275-282, and McMurry et al. (1997) Mol. Cell. Biol., Vol. 17 (8), 4553-4561. The applicant claims transgenic mice which have inactivated endogenous TCR loci, and whose genome contain transgenes composed of human T-cell

receptor loci, and methods of making said transgenic mice. The applicant further claims said mice and methods wherein the inactivated loci are endogenous TCR alpha and beta loci, wherein the transgenes comprises unrearranged V, D and/or J and C genes, and wherein the endogenous TCR loci have been inactivated by deleting the endogenous D, J, and or C genes.

Littman et al. teaches general methods for producing transgenic non-human animals, preferably mice, which express human lymphocyte transduction proteins and lack expression of the cognate murine lymphocyte transduction protein as a result of inactivation of the endogenous lymphocyte transduction gene loci (Littman et al., abstract, columns 4-6). Littman et al. further teaches that the lymphocyte transduction gene loci and lymphocyte transduction genes include the T cell receptor genes and particularly the T cell receptor alpha and beta gene products (Littman et al., columns 8-9). Littman et al. further provides substantial guidance for making transgenic mice which comprise a human lymphocyte transduction transgenes in their genome and which have inactivated cognate lymphocyte transduction transgenes (Littman et al., columns 14-36).

Littman et al. differs from the instant invention by not specifically describing a transgenic mouse in which the TCR loci are inactivated and human rearranged or unrearranged TCR V, D and/or J, and C genes have been inserted into the genome. It is noted that although Littman et al. suggests and provides motivation for inactivating the TCR loci of mice and inserting human TCR loci, Littman et al. exemplifies CD4 loci, not TCR loci. However, at the time of filing, transgenic mice which expressed unrearranged human T cell receptor loci and mice with have deletions in the endogenous TCR loci were described and available. Mombaerts et al. for instance teaches 3 different strains of mice which have inactivating deletions in the TCR alpha

loci, TCR beta loci, or TCR delta loci (Mombaerts et al., page 275). Mombaerts et al. also teaches double knock-out mice produced by crossing TCR beta and TCR delta knock-out mice (Mombaerts et al., page 275). McMurry et al. on the other hand teaches transgenic mice carrying the human TCR delta gene minilocus. McMurry et al. teaches that the human TCR delta gene minilocus comprises unrearranged human V, D, J, and C gene segments (McMurry et al., page 4553-4554). McMurry et al. teaches that these mice are capable of functionally rearranging the human TCR delta gene locus. Therefore, based on teaching of Littman et al. for making transgenic mice which contain a human lymphocyte transduction loci, such as the TCR loci, and in which the endogenous lymphocyte transduction loci is inactivated, it would have been *prima facie* obvious to the skilled artisan to breed the transgenic mice taught by McMurry with any of the TCR loci knock-out mice taught by Mombaerts et al. in order to produce a transgenic mouse in which the endogenous TCR alpha, and/or beta, and/or delta loci are inactivated and which contain the unrearranged human TCR delta loci. Further, based on the substantial direction provided by all of Littman et al., Mombaerts et al., and McMurry for making transgenic and knock-out mice, and the high level of skill in breeding and crossing mice, the skilled artisan would have had a reasonable expectation of success in making a transgenic mouse comprising an inactivated endogenous TCR loci and comprising a human TCR loci according to Littman et al. in view of Mombaerts et al.,and McMurry et al..

Claims 1-2, 5, 7-8, 30-31, 38-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over 5,859,312 (1/12/99), hereafter referred to as Littman et al. in view of Mombaerts et al. (1993) Cell, Vol. 75, 275-282, and Madsen et al. (1999) Nat. Genetics, Vol.

23, 343-347. The applicant claims transgenic mice which have inactivated endogenous TCR loci, and whose genome contain transgenes composed of human T-cell receptor loci, and methods of making said transgenic mice. The applicant further claims said mice and methods wherein the inactivated loci are endogenous TCR alpha and beta loci, wherein the transgenes comprises human TCR alpha and beta transgenes, and wherein the endogenous TCR loci have been inactivated by deleting the endogenous D, J, and or C genes.

Littman et al. teaches general methods for producing transgenic non-human animals, preferably mice, which express human lymphocyte transduction proteins and lack expression of the cognate murine lymphocyte transduction protein as a result of inactivation of the endogenous lymphocyte transduction gene loci (Littman et al., abstract, columns 4-6). Littman et al. further teaches that the lymphocyte transduction gene loci and lymphocyte transduction genes include the T cell receptor genes and particularly the T cell receptor alpha and beta gene products (Littman et al., columns 8-9). Littman et al. further provides substantial guidance for making transgenic mice which comprise a human lymphocyte transduction transgenes in their genome and which have inactivated cognate lymphocyte transduction transgenes (Littman et al., columns 14-36).

Littman et al. differs from the instant invention by not specifically describing a transgenic mouse in which the TCR loci are inactivated and human rearranged or unrearranged TCR V, D and/or J, and C genes have been inserted into the genome. It is noted that although Littman et al. suggests and provides motivation for inactivating the TCR loci of mice and inserting human TCR loci, Littman et al. exemplifies CD4 loci, not TCR loci. However, at the time of filing, transgenic mice which expressed unrearranged human T cell receptor loci and mice with have

deletions in the endogenous TCR loci were described and available. Mombaerts et al. for instance teaches 3 different strains of mice which have inactivating deletions in the TCR alpha loci, TCR beta loci, or TCR delta loci (Mombaerts et al., page 275). Mombaerts et al. also teaches making double TCR knock-out mice produced by crossing for instance TCR beta and TCR delta knock-out mice (Mombaerts et al., page 275). Madsen et al. further supplements the teachings of Littman et al. and Mombaerts et al. by teaching transgenic mice which comprise transgenes for the human TCR alpha and beta chains (Madsen et al., page 346). Madsen et al. further teaches that these mice express functional human TCR on mature T cells and respond to antigen (Madsen et al., page 343). It is also noted that Madsen et al. teaches crossing these transgenic mice with mice incapable of immunoglobulin or TCR rearrangement due to disruption of the RAG2 gene (Madsen et al., page 343). Therefore, based on teaching of Littman et al. for making transgenic mice which contain a human lymphocyte transduction loci, such as the TCR loci, and in which the endogenous lymphocyte transduction loci is inactivated, and the additional motivation provided by Madsen et al. for expressing human TCR transgenes in mice in which the endogenous TCR loci cannot rearrange, it would have been *prima facie* obvious to the skilled artisan to breed the transgenic mice expressing human TCR taught by Madsen et al. with any of the TCR loci knock-out mice taught by Mombaerts et al. in order to produce a transgenic mouse in which the endogenous TCR alpha, and/or beta, and/or delta loci are inactivated and which contain the unrearranged human TCR delta loci. Most particularly, since the transgenes of Madsen comprise the TCR alpha and beta genes, the motivation for inactivating the cognate loci in the mouse provided by Littman et al. would have made it *prima facie* obvious to the skilled artisan to specifically cross the mice of Madsen et al. with the mice which have inactivated

endogenous TCR alpha and beta loci. Further, based on the substantial direction provided by all of Littman et al., Mombaerts et al., and Madsen et al. for making transgenic and knock-out mice, and the high level of skill in breeding and crossing mice, the skilled artisan would have had a reasonable expectation of success in making a transgenic mouse comprising an inactivated endogenous TCR loci and comprising a human TCR loci according to Littman et al. in view of Mombaerts et al.,and Madsen et al..

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 30-31, 38-47, and 112-113 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The applicant claims transgenic mice which have inactivated endogenous TCR loci, and whose genome contain transgenes composed of human T-cell receptor loci, and methods of making said transgenic mice. The applicant further claims said mice and methods wherein the inactivated loci are endogenous TCR alpha and beta loci, wherein the transgenes comprises unrearranged V, D and/or J and C genes, and wherein the endogenous TCR loci have been inactivated by deleting the endogenous D, J, and or C genes. It is noted that the broadest claims read on the inactivation

of any TCR loci including the TCR delta or gamma loci, and that the human transgenes read on both rearranged and unrearranged human TCR loci.

The specification provides a prophetic description of how to inactivate the murine TCR alpha or murine TCR beta genomic locus using targeted homologous recombination. The specification further provides a prophetic description of how to make transgenic mice comprising portions of the unrearranged human TCR alpha or beta loci. The specification is silent regarding the TCR delta and gamma loci and fails to provide any description of targeting vectors for inactivating the endogenous murine TCR delta or gamma loci, or of transgenes, cosmids, or YACs comprising any portion of the human unrearranged or rearranged TCR delta or gamma loci. Regarding the human TCR alpha or beta loci, while the specification describes the unrearranged genomic loci of human TCR alpha and beta, it is silent in regards to any rearranged human TCR alpha or beta locus or methods of isolating and manipulating such rearranged loci. The applicant is reminded that 35 U.S.C. 112 requires that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991). Furthermore, the Federal Circuit has stated that:

> a specification need not disclose what is well known in the art. See, e.g., *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge

> of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.
> *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1005 (CAFC 1997)

Finally, it is noted that "case law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) 1970. By failing to provide any description for murine or human TCR delta or gamma loci, or for rearranged human TCR alpha or beta loci, or for any of the materials such as cosmids, primers, or vectors, necessary to isolate and manipulate such DNA sequences, the specification fails to provide an enabling disclosure for making transgenic mice with any inactivated endogenous TCR loci, or for making transgenic mice with any inserted human TCR loci. Thus, based on the lack of description provided by the specification as discussed above and the breadth of the claims, it would have required undue experimentation for the skilled artisan to make transgenic mice according to the instant invention in which the murine or human TCR loci are TCR delta or gamma loci, or wherein the human TCR loci is a rearranged human TCR alpha and/or beta loci.

The specification further fails to provide an enabling disclosure for transgenic mice which comprise unrearranged human TCR alpha or beta loci comprising a plurality of V, D and/or J, and C genes, and wherein the mice are capable of productively rearranging the human loci and producing mature T cells which express human TCR on the cell surface and respond to antigen. The specification teaches that the purpose for making the transgenic mice of the instant invention is for the production of human TCRs that are reactive with human antigens and thus can be used as therapeutic agents in human patients. As noted above, while the specification

provides a prophetic description for making a transgenic mouse with inactivated endogenous TCR alpha and beta loci and which comprises human unrearranged TCR alpha and beta loci, the specification provides not actual data for any mouse made according to the disclosed methods. At the time of filing, Madsen et al. teaches that even functional rearranged human TCR are difficult to express in mouse cells (Madsen et al., *supra*, page 343). Kouskoff et al. also states that at the time of filing, the construction and expression of TCR in mice was an "unwieldy endeavor" because of the size of the TCR genomic fragments and the lack of evidence as to which flanking sequences are required for proper expression (Kouskoff et al., 1995) J. Immunol. Methods, Vol. 180, 273-280, see page 274-275). Kouskoff et al. further teaches that the use of heterologous promoters to drive expression can lead to abnormal timing and regulation of TCR gene expression (Kouskoff et al., page 275). Thus, at the time of filing, it is clear that even the expression of rearranged heterologous TCR in mice was considered difficult and unpredictable. The expression of functional TCR from unrearranged genomic DNA adds an extra level of complexity to the equation and thus increases the unpredictability of achieving successful functional TCR expression on mature T cells in the periphery. Based on the level of difficulty in expressing heterologous and particularly human TCR in murine cells, the lack of any evidence in the specification that a mouse made using the described vectors would in fact be capable of rearranging and expressing functional TCR on the cell surface capable of passing both positive and negative selection, and the breadth of the claims, it would have required undue experimentation for the skilled artisan to make the instant invention as claimed.

Further, T cell maturation involves not only the rearrangement of the TCR genes in the developing T cell, but also successful completion of T cell negative and positive selection in the

thymus. In particular, failure to achieve positive selection results in T cell death. Selection in the thymus is mediated by cell-cell contact of the immature T cell with resident thymocytes. Cell-cell contact is mediated by the interaction of cell surface TCR on the immature T cells with peptide/MHC and CD4 or CD8 on the thymocytes. In the absence of human MHC molecules and human CD4 or CD8 on the thymocytes, it is unclear whether the immature T cells expressing human TCR would successfully pass positive and negative selection. Further, were any T cells to reach the periphery, these T cells would have been selected based on binding to murine MHC and CD4 or CD8. Thus, the "human" TCR on any such peripheral murine T cells would be unlikely to recognize or bind to human peptide MHC complexes. As a result, such "human" TCR would be no more useful as therapeutics in humans than murine TCR. Thus, in view of the high degree of unpredictability in achieving successful expression of functional heterologous TCR in mice, the complexity of T cell maturation, and importance of TCR/MHC interaction during positive and negative selection in the thymus, the skilled artisan would not have been able to predict without undue experimentation whether any mature T cells would be produced in a transgenic mouse according to the instant invention as claimed.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. For all official communications, the

technology center fax number is (703) 872-9306. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER